

*REMARKS/ARGUMENTS*

Claims 9-11 have been objected to as depending from canceled claim 1. Accordingly, claims 9-11 have been amended to depend from claim 8, thus correcting an obvious clerical error. No new matter has been added thereby. Withdrawal of this objection is respectfully requested.

Claims 8-12 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Raffa et al. (EP 0 546 676) and Caruso (U.S. 5,919,826), and further in view of Saslawski et al. (U.S. 6,372,255), Forrest et al. and Physicians' Desk Reference ("PDR"). Applicants maintain that the prior art does not teach or suggest a method of treating pain with a pharmaceutical composition that includes the *specific* combination of ketorolac tromethamine and tramadol hydrochloride.

The cited references do not teach or suggest treating pain with ketorolac tromethamine and tramadol hydrochloride, specifically, and much less treating pain with, e.g., 0.0010 g to 0.1000 g of ketorolac tromethamine and 0.0010 g to 0.2000 g of tramadol hydrochloride as recited in claim 9, or with, e.g., ketorolac tromethamine and tramadol hydrochloride, colloidal silicate dioxide, sodium glycolate starch, lactose, microcrystalline cellulose and magnesium stearate as recited in claims 11 and 12. Further, the cited references do not teach or suggest that the specific combination of ketorolac tromethamine and tramadol hydrochloride would produce a synergistic effect as Applicants have discovered. The fact that the recited combination exhibits good efficacy at very low doses, as Applicants have shown, highlights the unexpected synergy exhibited by the recited combination. This synergy, which was subsequently documented in López-Muñoz et al., *Eur. J. Pharmacol.*, 2004, 484: 157-165 as addressed in Applicants' previous responses, would not have been predicted based on the teachings of the cited references, individually or combined.

The fact that Raffa et al. and Forrest et al. disclose synergy with respect to certain combinations of opioids and NSAIDs does not suggest that the *specific* combination of ketorolac tromethamine and tramadol hydrochloride would have produced a synergistic effect, particularly when García-Hernández et al, *Pharmacology, Biochemistry, and Behavior*, 2007, 87:331-340, the pending publication of which was submitted and addressed in Applicants previous responses, teaches that combining tramadol and rofecoxib (a NSAID)

failed to produce a synergistic effect. Moreover, Caruso teaches that a synergistic effect is observed with combinations of tramadol and NMDA receptor antagonists, yet regards NSAIDs (including ketorolac) as purely optional (e.g., col. 6, lines 13-25) and completely fails to appreciate the synergistic effect exhibited by the specific combination of ketorolac tromethamine and tramadol hydrochloride. As such, Raffa et al., Caruso and Forrest et al., alone or in combination, would not have taught or suggested treating pain with the specific combination of ketorolac tromethamine and tramadol hydrochloride, as recited in the instant claims.

Saslawski et al. was cited as disclosing excipients used in oral compositions, and the PDR was cited as disclosing salt forms of tramadol and salt forms of ketorolac. Saslawski et al. discloses multilayer tablets, e.g., bilayer tablets (e.g., col. 2, lines 12-15), wherein each layer may contain a different active ingredient (col. 2, lines 52-53). The disclosed tablets include a first layer that disintegrates rapidly upon administration, and a second layer, which, by contrast, is not biodegradable and serves to promote prolonged release (col. 2, lines 25-31). However, neither Saslawski et al. nor PDR teaches or suggests a method of treating pain with the specific combination of ketorolac tromethamine and tramadol hydrochloride, in the ratios, amounts or otherwise as recited in the instant claims. As such, Saslawski and PDR, alone or in combination, with each other or with any of the other cited references, do not render obvious any of the instant claims.

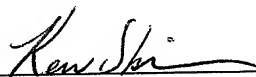
A judgment on obviousness may involve a reconstruction based on hindsight reasoning so long as it does not rely on knowledge gleaned only from applicant's disclosure (M.P.E.P. § 2145(X)(4)). Nevertheless, "[d]etermination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998). Further, "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). In the instant case, the Office appears to have engaged in the piecing together of isolated disclosures from the prior art to arrive at the claimed invention using Applicants' disclosure as a guide, which is impermissible.

In view of the foregoing, the cited references, when properly considered as a whole, would not have rendered obvious the claimed invention. Withdrawal of the obviousness rejection is respectfully requested.

*Conclusion*

Applicants respectfully submit that the present application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



---

Kenneth P. Spina, Reg. No. 43,927  
LEYDIG, VOIT & MAYER, LTD.  
Two Prudential Plaza, Suite 4900  
180 North Stetson Avenue  
Chicago, Illinois 60601-6780  
(312) 616-5600 (telephone)  
(312) 616-5700 (facsimile)

Date: November 18, 2008